(19) FEDERAL REPUBLIC OF GERMANY

GERMAN PATENT OFFICE

(12) **Unpublished Patent Application**

(10) **DE 38 36 862 A1**

(21) File No.: P 38 36 862.5
(22) Date of application: 10/27/88
(43) Date of publication: 5/3/90

(51) Int. Cl[5]:
A 61 K 31/565
// C07J 1/00
(A61K 31/565,31:23)

DE 38 36 862 A1

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(54) Composition for Transdermal Administration of Steroid Hormones

A composition for transdermal application of steroid hormones is described. The composition is characterized in that the steroid hormone is dissolved in a fatty acid ester of the general formula
CH_3-$(CH_2)_n$-COOR

n being a number from 8 to 18 and
R being an alkyl radical having a maximum of 6 carbon atoms.

DE 38 36 862 A1

DE 38 36 862 A1

Specification

This invention relates to a composition for transdermal application of steroid hormones, which is characterized in that the steroid hormone is dissolved in a fatty acid ester of the general formula

CH_3-$(CH_2)_n$-COOR

n being a number from 8 to 18 and
R being an alkyl radical having a maximum of 6 carbon atoms.

It is known that drugs administered transdermally have the advantage that they make possible a more uniform release of the active ingredient over an extended period of time than is possible, for example, with drugs administered orally. However, for non-readily water soluble active ingredients of drugs such as steroid hormones, for example, it is quite difficult to create transdermal systems that ensure an adequate penetration of the active ingredient through the skin for therapy.

It has now been found that using the composition of the present invention surprisingly makes it possible to achieve a significantly higher penetration rate of the steroid hormones through the skin than is possible with the known transdermally administered drugs containing steroid hormones.

Suitable steroid hormones for the composition of the present invention are pharmacologically active steroids that are used as active ingredients. Such steroid hormones [are] in particular estrogen, gestagenically, androgenically or anabolically active steroids or combinations of the same. Such steroids are, for example, the estrogen estradiol as well as estriol and their esters, such as valerate, benzoate or undecylate, the estrogen ethinylestradiol, the gestagens norethisterone acetate, levonorgestrel, chlormadinone acetate, cypoterone acetate, desorgestrel or gestodone, the androgen testosterone or its esters (propionate, undecylate, etc.) and the anabolics methandrosterone or nandrolone and its esters.

Fatty acid esters that are suitable for the composition of the present invention are, for example, those of lauric acid, myristic acid, stearic acid and palmitic acid such as, for example, the methyl esters, ethyl esters, propyl esters, isopropyl esters, butyl esters, sec-butyl esters, isobutyl esters of these acids.

Esters preferred in particular are those of myristic acid, such as its methyl ester and in particular its isopropyl ester. It need not be explained in greater detail that mixtures of these fatty acid esters are also suitable for the composition of the present invention.

The concentration in which the steroid hormone or the steroid hormones are optimally dissolved in the fatty acid ester is of course a function of the type of active ingredient used and the intended single dose; in the individual case, it must be determined using preliminary tests known to a person skilled in the art such as, for example, the determination of the attainable blood plasma concentrations of active ingredient in selected compositions of the present invention. In general, active ingredient concentrations of 0.2 to 20 weight percent in the composition of the present invention are adequate, where the saturation concentration of the active ingredient present in the composition can also, of course, be the possible maximum.

The rate of the percutaneous absorption through the composition of the present invention may, for example, be determined using radioactively marked steroid hormones.

Freshly prepared skin from the abdomen of hairless mice, which has been freed of subcutaneous fat, is stretched in a Franz diffusion cell containing isotonic propylene glycol (MG 400) or phosphate buffer of pH 7. Then, 2 µl test solution is poured onto the skin and the content of the steroid hormone reaching the collecting liquid after 24, 48 and 72 hours is determined by liquid scintillation counting.

The following tests were performed:

A: a 10 weight percent solution of estradiol in isopropyl myristate
B: a 10 weight percent solution of estradiol in propylene glycol
C: a 2 weight percent solution of gestodene in isopropyl myristate
D: a 2 weight percent solution of gestodene in propylene glycol.

The following table shows the results obtained in these tests:

Table

Penetration flow in ng steroid per cm^2 skin surface and hours

Time interval	Test A	Test B	Test C	Test D
00-24 hr	594 ± 24	490 ± 135	546 ± 10	209 ± 63
24-48 hr	429 ± 39	139 ± 23	379 ± 14	62 ± 26
48-72 hr	337 ± 39	114 ± 17	287 ± 15	59 ± 29

These results show that the use of the composition of the present invention is able to increase the penetration flow of the steroid hormones through the skin significantly.

For the manufacture of pharmaceutical products, the customary adjuvants such as bactericides or aromatic principles may be added to the solutions of the present invention and filled into customary dosing containers. However, it is also possible to emulsify these solutions with an aqueous phase after the addition of emulsifiers in order to produce lotions, cremes or salves. Furthermore, with the addition of a propellant gas, it is possible to produce sprays that may be filled into the customary dosing containers. It may also be mentioned that the solutions of the present invention may be processed into active ingredient-containing patches or bandages using silicone elastomers (DE-A 31 31 610, UP-A 39 96 934 und US-A 4,336,243).

The medical indication of the composition of the present invention is the same as for the known pharmaceutical preparations containing the same steroid hormones as the active ingredient.

The following exemplary embodiments are used to explain the composition of the present invention in greater detail.

Example 1

100.00 g estradiol is dissolved in 1000 g isopropyl myristate, sterile filtered and filled into 5 ml vials under sterile conditions.

The composition may be used to treat menopausal symptoms.

Example 2

20.00 g gestodene is dissolved in 1000 g isopropyl myristate, sterile filtered and filled into 5 ml vials under sterile conditions.

The composition may be used for monohormonal contraception.

Claim

A composition for transdermal application of steroid hormones, **characterized in** that the steroid hormone is dissolved in a fatty acid ester of the general formula

CH_3-$(CH_2)_n$-COOR

n being a number from 8 to 18 and
R being an alkyl radical having a maximum of 6 carbon atoms.

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Certificate of Accuracy

This is to certify that the attached document, Unpublished Patent Application DE3836862A1, originally written in German is, to the best of our knowledge and belief, a true, accurate and complete translation into English.

Dated: January 10, 2005

Ashley L. Schroeder
Legal Team Manager, Translations
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Sworn to and signed before
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January, 2005

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No. 01AL6004438 Qualified in Kings County
Certificate Filed in New York County
Commission Expires: 3/[illegible]/2006